REMARKS

Claims 1, 3-32, 34-47, 59, 61-64 and 144-147 are pending in this application. Claims 15-29 and 34-47 are allowable. Claim 1 is amended herein for clarity. It respectfully is submitted the amendment of claim 1 should place the application into condition for allowance. It appears that maintenance of the rejection is based on the inadvertent omission of a word "second" from the second alternative in claim 1. Claim 1 as amended addresses this omission. As discussed below and previously, this amendment is introduced to advance the application to issue, but applicant does not consider it warranted.

THE REJECTION OF CLAIMS 1, 3, 4, 6, 7, 9, 10-14, 30-32 34, 35, 41-43 AND 47 UNDER 35 U.S.C. §102(b)

Claims 1, 3, 4, 6, 7, 9, 10-14, 30-32 34, 35, 41-43 and 47 are rejected under 35 U.S.C. §102(b) as being anticipated by Marschall *et al.* as evidenced by LIPOFECTAMINE Reagent or TRANSFECTAM Reagent product description. The Examiner urges that Marschall *et al.* discloses introducing large nucleic acid molecules into cells by lipofection and that the product descriptions for LIPOFECTAMINE and TRANSFECTAM includes replacing the serum with serum-free medium. As in the rejection over Unger *et al.*, the Examiner is relying upon an expensive interpretation of delivery agent as including the medium in which the cells are contacted. As argued above, this interpretation is untenable. Accordingly, this rejection respectfully is traversed.

It is noted that the rejection appears to be maintained because of the inadvertent lack of clarity of claim 1(b). As amended herein, it should be clear that it is the second delivery agent that is applied to the cell and that the second delivery agent is one that enhances permeability of the cell.

Notwithstanding this, the Examiner also failed to provide documentation to support that it increases permeability of cells. Serum free medium is employed to suspend cells and to maintain their viability; there is no evidence of record that serum free medium enhances contact of a nucleic acid with a cell or increases permeability of cell. As discussed in the previous response, serum free medium is employed with a delivery agent, such as LIPOFECTAMINE, and is not, by itself, something that delivers a nucleic acid molecule into a cell. The instructions for use of LIPOFECTAMINE and for TRANSFECTAM specifically require suspension of cells in serum free medium; there is no evidence of record that one of ordinary skill in the art would consider serum free medium to be a delivery agent by itself.

The application describes the use of two delivery agents, and exemplifies using LIPOFECTAMINE as **one of the agents**. Using LIPOFECTAMINE in accord with the manufacturer's instructions **does not constitute** use of two reagents.

Hence, Applicant maintains that the Examiner's interpretation of delivery agent as including the medium in which a cell is suspended, merely because it includes some components in common with delivery agents is untenable and unsupported. Merely because serum free medium includes some components that are, when applied in high concentrations, delivery agents, does not make serum free medium a delivery agent within the scope of any definition of a delivery agent. Serum free medium is not and would not be recognized by any one of ordinary skill in the art to constitute a delivery agent; the Examiner as provided no evidence that serum free medium delivers nucleic acid molecules into cells. As discussed in the previous response and below, suspension in serum free medium is part of the manufacturer's protocol for applying a commercial delivery agent. Addition of serum free medium is part of the protocol for adding a cationic amine to cells. It serves as the medium in which cells are suspended for addition of the cationic amine; there is nothing to indicate that the medium serves as a delivery agent; it is not a separate delivery. As interpreted by the Examiner, the claims, as previously pending, read on addition of a single delivery agent. The specification and claims render it clear that two reagents are required.

CLAIMS

Independent Claim 1 is directed to a method for introducing a large nucleic acid molecule into a cell by:

(a) contacting a large nucleic acid molecule with a first delivery agent;

(b) contacting adding a second delivery agent to a composition containing the a cell with a delivery agent or applying a **second** delivery agent to the cell, whereby the second delivery agent contacts the cell; and

(c) contacting the cell with the nucleic acid molecule, whereby the nucleic acid molecule is delivered into the cell.

Steps (a) and (b) are performed sequentially in any order , provided that if the delivery agent is energy it is not applied to the nucleic acid molecule and it is not applied to the cell after contacting the cell with the nucleic acid molecule. The first and second delivery agents are different; the first delivery agent increases contact between the nucleic acid molecule and the cell compared to in the absence of the delivery agent; and the second

delivery agent enhances permeability of the cell compared to prior to addition of the second delivery agent to the composition. Dependent claims recite additional elements.

The claim is amended herein in step b) to render it clear that step b refers to a "second" delivery agent. As recited in claim 1, the first and second delivery agents are different; the first delivery agent increases contact between the nucleic acid molecule and the cell compared to in the absence of the delivery agent; and the second delivery agent enhances permeability of the cell compared to prior to addition of the second delivery agent to the composition.

As discussed previously, the application and rejected claims render it clear that there are two treatments required; this cannot include the cells in their medium as that contradicts the specification and intended elements of the method. As discussed above, the specification clearly states that the methods for delivery include affirmative addition of two agents. For these claims, one agent is intended to increase contact of the nucleic acid molecule with a cell. Exemplary of such agents are cationic lipids, such as LIPOFECTAMINE, not cell culture medium nor other medium in which such contacting occurs. The second agent is one, such as energy that increases permeability of the cells. Nothing in the specification nor known to those of ordinary skill in the art would lead one of ordinary skill in the art to consider serum free medium to be an agent that increases permeability of cells; rather it is for suspending cells to maintain viability.

Relevant law

Relevant law is provided in previous responses of record and is incorporated herein by reference.

Disclosure of Marschall *et al.* and differences from the instant claims

Marschall *et al.* discloses transfection of YACS into cells using a single cationic amine. Marschall *et al.* does not describe a method in which nucleic acid molecules are contacted with a delivery agent and in which a delivery agent is added to a composition containing cells. As in the previous response, addition of serum free medium is part of the protocol for adding a cationic amine to cells. It serves as the medium in which cells are suspended for addition of the cationic amine; there is nothing to indicate that the medium serves as a delivery agent. Further, in the interest of advancing prosecution, claim 1, as amended recites that the first delivery agent increases contact of the nucleic acid with the cell, which cationic amines do; and the second delivery agent increases permeability of the cells.

Not only is serum free medium not a delivery agent, there is no evidence provided that it increases permeability of cells. Serum free medium is employed to suspend cells and to maintain their viability Again, the Examiner is reminded MPEP 2144.03 states:

> The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well- known" in the art. In re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). . . ..

The statement by the Examiner that the serum free medium in which the cells are suspended increases permeability is not capable of instant and unquestionable demonstration. MPEP 2144.03 continues:

> If justified, the examiner should not be obliged to spend time to produce documentary proof. If the knowledge is of such notorious character that official notice can be taken, it is sufficient so to state. In re Malcolm, 129 F.2d 529, 54 USPQ 235 (CCPA 1942). If the applicant traverses such an assertion the examiner should cite a reference in support of his or her position.

In this instance, there is no evidence serum-free medium is used to increase permeability of cells nor evidence that such knowledge is notorious.

Analysis

Marschall *et al.* does not disclose a method for delivering large nucleic acid molecules into cells by contacting nucleic acid molecules with a first delivery agent that increases contact of cells with nucleic acids; and contacting the cells with a second agent that increases their permeability to the nucleic acid molecule. Marschall *et al.* discloses a method in which commercially available delivery agents are used to introduce YACS into cells. As described in the instant application, protocols for use of these commercially available cationic amines include suspending cells in serum free medium; such step does not constitute addition of a second delivery agent, and certainly not one that increases permeability of cells to the nucleic acid molecules. Thus, Marschall *et al.* does not anticipate any of the rejected claims.

Furthermore as stated previously, an anticipatory publication must describe the claimed invention with sufficient clarity and specificity so that one skilled in the relevant art could practice the subject matter of the patent without assistance from the patent claimed to have been anticipated Columbia Broadcasting System v. Sylvania Elec. Products, Inc., 415 F.2d 719, 735, 162 USPQ 577 (1st Cir.1968) cert. denied, 396 U.S. 1061, 164 USPQ 321 (1970). In this instance, it is only by reading Marschall *et al.* with assistance from the instant application that one of skill in this art could practice the claimed method, which

requires treatment of nucleic acid molecules with a contact-enhancing delivery agent, such as a cationic amine, and treatment of the cells with an agent that increases permeability. Marshall *et al.* discloses use of a single delivery agent; not two as required by the instant claims. Nothing in Marschall *et al.* or of record would place one of ordinary skill in the art in possession of a method that requires addition of a second delivery agent to cells to increase their permeability.

THE REJECTION OF CLAIMS 1-10, 12-14, 30-32, 59, 61-64 and 144-147

Claims 1-14, 30-32, 59, 61-64 and 144-147 are rejected under 35 U.S.C. §103(a) as being upatentable over the Hadlaczky *et al.* (U.S. Patent No. 6,025,155), which teaches lipid-mediated transfection, in view of Marschall *et al.* as evidenced by LIPOFECTAMINE Reagent or TRANSFECTAM Reagent because Hadlaczky *et al.*, describes introduction of artificial chromosomes, including ACES, into cells using lipid mediated transfer; and Marschall *et al.* teaches use of the commercially available cationic amines, LIPOFECTAMINE and TRANSFECTAM for introduction of YACS into cells. The Examiner concludes that it would have been obvious to have used LIPOFECTAMINE or TRANSFECTAM for lipid-mediated transfection of large nucleic acid molecules, such as ACES into cells. This rejection is respectfully traversed.

As with the rejections above, this rejection is premised on the assertion that serum free medium constitutes a delivery agent and is maintained because of the inadvertent omission of "second" in claim 1 step (b). Accordingly the rejection should be obviated by the amendment herein.

Relevant law

The relevant law for establishing a *prima facie* case of obviousness is set forth in previous responses and is incorporated herein by reference.

Analysis

The combination of teachings of Hadlaczky *et al.* and Marshall *et al.* does not result in the instantly claims methods

As discussed above, a delivery agent is a something that facilitates introduction of nucleic acid into a cell, such as by enhancing contact of nucleic acids with cells and/or increasing the permeability of cells to nucleic acids compared to its absence. The medium in which the cells are contacted does not meet this definition nor the understanding of those of

skill in the art nor other disclosure in the application. The Examiner has provided no evidence to support such assertion.

Hadlaczky *et al.* teaches the use of lipid mediated transfection for introducing large nucleic acid molecules into cells. Marschall *et al.* teaches the use of the cationic amines LIPOFECTAMINE and TRANSFECTAM for introducing YACS into cells. Neither references teaches or suggest a method in which nucleic acid molecules are treated with a first delivery agent that increases contact between the nucleic acid molecules and the cells (compared to in its absence) , and cells are treated with a second, different reagent, that increases permeability of the cells (compared to in its absence). Therefore, the combination of teachings of these references cannot result in the instantly claimed methods, which require these elements. Thus, the Examiner has failed to set forth a *prima facie* case of obviousness.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,

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